2) Primary Neoplasm (Table 13, mid-panel)

As shown, the primary neoplasm reported with the highest incidence was lung cancer. This occurred in 60% of OND and 58% of the GRAN patients. Other types of tumors were reported but at lower rates, with no other tumor type occurring in more than 10% of the patients.

3) Concurrent Illness (table 13, lower panel)

- 93% of the OND and 94% of the GRAN patients had at least one concurrent medical condition other than their primary cancer. Concurrent cardiovascular conditions occurred in about one-half of all patients (188), although respiratory, musculoskeletal, and gastrointestinal were among other commonly occurring conditions. Concurrent medical conditions were similar between both treatment groups.

Distribution of Chemotherapeutic Regimens (Table 14, upper panel)

- In addition to cisplatin (or carboplatin), both treatment groups received concomitant chemotherapy which included

etoposide	(48%)
methotrexate	(6%), and
5-FU	(12%).

- There were no significant differences between the two treatment groups.

[See Table 12, for information on cisplatin dosing.]

4) Concurrent Medications (Table 14, lower panel)

There were no significant differences between the two treatment groups with regard to concurrent medications.

TABLE 13
Study S3AA3004/3007 (Report RM1997/04252/00)

PATIENT DEMOGRAPHICS AND DISEASE BASELINE CHARACTERISTICS

	OND 24 mg QD PO	GRAN 10 μg/Kg I.V.
Number of subjects	[n=184]	[n=187]
I. DEMOGRAPHICS		
Age (y)		
Mean (STD)	63.8 (10.6)	64.3 (11.0)
Median	65	66
Min-Max	32-86	38-86
Height (cm)	169.4 (10.6)	169.4 (10.3)
Weight (Kg)		
Mean (STD)	72.3 (16.9)	72.8 (17.7)
Min-Max	31-125	37-138
Gender		
F	79/184 (43%)	86/187 (46%)
M	105/184 (57%)	101/187 (54%)
Race		
Black	18/184 (10%)	12/187 (6%)
Hispanic	1/184 (<1%)	2/187 (1%)
Oriental	2/184 (2%)	0/187
Caucasian/White	161/184 (88%)	172/187 (92%)
Other	2/184 (1%)	1/187 (<1%)
II. PRIMARY NEOPLASM		
Lung	111 (60%)	109 (58%)
Small cell cancer of lung	36 (20%)	34 (18%)
Adenocarcinoma of lung	29 (16%)	27 (14%)
Large cell cancer of lung	15 (8%)	23 (12%)
Squamous cell cancer of lung	14 (8%)	12 (6%)
Non-small cell carcinoma of lung	10 (5%)	7 (4%)
Gynecologic	18 (10%)	19 (10%)
Genito-urinary	17 (9%)	16 (9%)
Cancer of bladder	13 (7%)	14 (7%)
Gastrointestinal	15 (8%)	15 (8%)
Cancer of esophagus	10 (5%)	10 (5%)
Head and Neck	15 (8%)	11 (6%)
Other	6 (3%)	6 (3%)
Skin	1 (<1%)	6 (3%)
Bone and Soft Tissue	1 (<1%)	2 (1%)
Thorax	0	3 (2%)
III. CURRENT MEDICAL CONDITION		
Number of subjects with current medical condition	172 (93%)	176 (94%)
Cardiovascular	90 (49%)	98 (52%)
Respiratory	90 (49%)	95 (51%)
Muculoskeletal	68 (37%)	79 (42%)
Gastrointestinal	60 (33%)	65 (35%)
Non-site specific	44 (24%)	42 (22%)
Endocrine and metabolic	42 (23%)	41 (22%)
Ears, Nose and Throat	35 (19%)	(19%)

TABLE 14
Study S3AA3004/3007 (Report RM1997/04252/00)

CHEMOTHERAPEUTIC REGIMENS AND CONCURRENT MEDICATIONS

	OND 24 mg QD PO [n=184]	GRAN 10 μg/Kg I.V. [n=187]
I. DISTRIBUTION OF CHEMOTHERAPEUTIC REGIMENS		
Cytotoxics & Anti-Neoplastics	184 (100%)	187 (100%)
Cisplatin	184 (100%)	186 (>99%)
Etoposide	91 (49%)	87 (47%)
Fluorouracil	26 (14%)	20 (11%)
Vinblastine sulphate	10 (5%)	14 (7%)
Methotrexate	12 (7%)	10 (5%)
Vinorelbine tartrate	7 (4%)	11 (6%)
Vinblastine	9 (5%)	9 (5%)
Doxorubicin hydrocloride	11 (6%)	6 (3%)
Mitomycin	6 (3%)	8 (4%)
Paclitaxel	3 (2%)	5 (3%)
Cyclophosphamide	5 (3%)	1 (<1%)
Doxorubicin	4 (2%)	2 (1%)
Gemcitabine	3 (2%)	1 (<1%)
Vincristine	0	1 (<1%)
Carboplatin	0	1 (<1%)
Nutrition	3 (2%)	1 (<1%)
Folinic acid	3 (2%)	1 (<1%)
II. CONCURRENT MEDICATION		
Number with concurrent medication	181 (98%)	180 (96%)
Cardiovascular System	146 (79%)	150 (80%)
Mannitol	92 (50%)	98 (52%)
Frusemide	75 (41%)	77 (41%)
Digoxin	16 (9%)	13 (7%)
Nifedipine	9 (5%)	11 (6%)
Atenolol	10 (5%)	10 (5%)
Warfarin sodium	9 (5%)	7 (4%)
Diltiazem hydrochloride	10 (5%)	5 (3%)
Drugs Acting Via the Nervous System	127 (69%)	128 (68%)
Paracetamol	27 (15%)	16 (9%)
Aspirin	24 (13%)	18 (10%)
Salbutamol sulphate	15 (8%)	18 (10%)
Morphine sulphate	9 (5%)	16 (9%)
Percocet	17 (9%)	8 (4%)
Temazepam	10 (5%)	10 (5%)
Ipratropium bromide	10 (5%)	8 (4%)
Tylenol No. 3	8 (4%)	9 (5%)
Alprazolam	3 (2%)	11 (6%)
Theophylline	11 (6%)	3 (2%)
Nutrition	103 (56%)	113 (60%)
Potassium chloride	97 (53%)	103 (55%)
Vitamin E	6 (3%)	6 (3%)
Multivitamins	4 (2%g)	3 (2%)
Gastrointestinal System	96 (52%)	96 (51%)
Magnesium sulfate	58 (32%)	65 (35%)
Docusate sodium	22 (12%)	16 (9%)

Ranitidine hydrochloride	6 (3%)	12 (6%)
Cimetidine	8 (4%)	4 (2%)
Omeprazole	7 (4%)	3 (2%)
Nizatidine	6 (3%)	3 (2%)
Endocrine & Metabolic	54 (29%)	51 (27%)
Allopurinol	7 (4%)	7 (4%)
Thyroxine sodium	9 (5%)	4 (2%)
Conjugated estrogens	3 (2%)	8 (4%)
Magestrol acetate	7 (4%)	2 (1%)
Anti-Infective & Immunologicals	24 (13%)	27 (14%)
Various Drugs	11 (6%)	24 (13%)
Cytotoxics & Anti-Neoplastics	5 (3%)	7 (4%)
Skin, Ear & Eye Preparations	2 (1%)	6 (3%)
Oxygen	1 (<1%)	1 (<1%)

e. Clinical Response

1) Analysis of Primary Efficacy Parameters

a) Complete Response (Table 15)

- In the ITT analysis of CR, the difference between the two treatment groups (7% in favor of OND) was not statistically significant. As illustrated in the upper panel of Table 15, a 95% CI on the difference in CR rates was –4% to 17% (the CI crossed zero).

- Similarly, in the Per-Protocol analysis, the difference between the two treatment groups (7% in favor of OND) was not statistically significant. Once again and as illustrated in the lower panel of Table 15, a 95% CI on the difference in CR rates was –3%, 18%.

TABLE 15

Study S3AA3004/3007 (Report RM1997/04252/00)

CLINICAL RESPONSE – ANALYSIS OF PRIMARY EFFICACY PARAMETER COMPLETE RESPONSE

RESPONSE BY TREATMENT GROUP			THERAPEUTIC GAIN (%) / (95% CI/[p-value][a]
I. Intent-to-Treat Analysis [n=371]			
OND 24 mg QD PO [n=184]	**GRAN 10 μg/Kg I.V. [n=187]**		
106 (58%)	95 (51%)		7% (-4%, 17%) [N.S.]
II. PER-PROTOCOL ANALYSIS [n=341]			
[n=171]	[n=170]		
99 (58%)	86 (51%)		7% (-3%, 18%) [N.S.]

Reviewer's Table

a) p-values and estimates from Mantel-Haenszel test.

b) Complete Response by Subgroups

The sponsor analyzed CR rates by gender and presented the results of this analysis in their Table 10.4 (p. 99 of the Clinical Report). Complete responders were 46% females vs 67% males in the OND treatment group and 41% vs 59% in the GRAN group, respectively. Although – as shown in other trials – females were less likely to respond to anti-emetic treatment, there was no difference between the treatment groups for either males or females.

c) Complete Response by Site

The response by site was summarized in sponsor's Table 10.5 (data not presented in the current review). Participating investigators enrolled between 1 and 60 patients per site. Of these, 12 investigators enrolled 11 patients or more. The CR rates at these 12 sites were:

	OND 24 mg QD PO [n=184]	GRAN 10 μg/Kg I.V. [n=187]
Spector	21/30 (70%)	21/30 (70%)
Lester	12/20 (60%)	9/20 (45%)
Harvey	7/16 (44%)	7/16 (44%)
Chevlen	8/14 (57%)	6/16 (38%)
Sciortino	5/13 (38%)	6/12 (50%)
Whaley	3/9 (33%)	7/9 (78%)
Madajewicz	5/8 (63%)	3/8 (38%)
Isaacs	5/8 (63%)	4/7 (57%)
Homesley	4/7 (57%)	2/8 (25%)
Yee	3/6 (50%)	4/8 (50%)
Beck	4/6 (67%)	2/6 (33%)
Tchekmedyian	2/5 (40%)	4/6 (67%)

As shown, the CR rates were between 33% and 70% for OND and between 25% and 70% for i.v. GRAN. With a few exceptions (i.e. Whaley, Homesley, and Beck) the CR rates were similar for each treatment group. Actually, the CR rate for each treatment group was identical in 3 of these 12 sites: Yee (50% in each treatment group), Harvey (44% in each treatment group) and especially Spector, the site with the highest enrollment, 30 patients per group (CR-70% in each treatment group).

2) Analysis of Secondary Efficacy Parameters

- [Therapeutic failure rates by investigator were presented in sponsor's Table 10.5 (p. 100 through 107 of the Clinical Report)].

  - There were 50 OND subjects (27%) and 65 GRAN subjects (35%) that met the definition of therapeutic failure. Similarly, 27% of the ondansetron-treated subjects and 34% of the granisetron-treated subjects received rescue

medication. These two proportions were similar since the majority of subjects defined as therapeutic failures also received rescue medication.

- There were no statistically significant difference between the treatment groups in terms of the percentage of subjects considered therapeutic failures (p=0.114), or in terms of the percentage of subjects receiving rescue medication (p=0.112).

- [The percentage of subjects with either a complete or major response were summarized in sponsor's Table 10.1.]

  - The difference in the percentage of subjects with either a complete or major response (68% for OND and 61% for GRAN patients) was not statistically significant (p=0.131).

- [Time to treatment failure was summarized in sponsor's Table 11 and Fig. 1.]

  - There was no statistically significant difference between treatment groups in their time to treatment failure (p=0.148). Of those subjects who did fail treatment, few did so within the first 3 h; most did so between 6 and 24 h after the start of chemotherapy.

- [Patients' nausea assessments were summarized in sponsor's Table 12 (p. 109 through 114 of the Clinical Report)].

  - The nausea assessments were similar between the treatment groups at all time points.

    Only 17 subjects reported any nausea at baseline. The biggest difference between treatment groups was at the 24-h assessment, where 10% fewer subjects in the OND group reported no nausea than in the GRAN group (56% vs 46%, respectively).

  - 43% of the OND and 35% of the GRAN patients completed the trial without nausea or rescue medication. The difference between the treatment groups was not statistically significant (p=0.095, 95% confidence interval on the difference was –1% to 18%).

- The average of all the post-treatment nausea scores was 1.4 (scale of 0-10) for the OND treatment group and 1.8 for the GRAN group, including a low overall level of nausea. This includes the post-withdrawal scores that were assigned a score of 10 in this analysis. This difference was not statistically significant (p=0.242).

f. Safety Evaluations (Table 16)

The main conclusion from these evaluations is that a single 24 mg orally administered dose of OND is well-tolerated. The safety profile of this dose level of the drug is smiliarly that of 10 μg/Kg of intravenously administered GRAN.

All 373 patients who were exposed to test medication (OND=184; GRAN=187)[20] were used in these analyses. The two treatment groups were similar with respect to all the variables listed in Table 16. The median dose of cisplatin (70 mg/m^2) and the median time of cisplatin infusion (2h) was the same for both treatment groups. Deaths, serious AEs and withdrawals due to AEs were considered not related to test medication. The treatment groups were comparable to each other in the proportion of patients reporting one or more AE, the most commonly reported AE (headache) and the proportion of patients with treatment-related AEs.

The two treatment groups were similar to each other with respect to transitions in laboratory parameters and in laboratory values considered by the investigator to be clinically significant. Analyses based on threshold laboratory values revealed that the majority of outlier values occurred with lymphocytes and neutrophils and were similar between the two treatment groups. A significant decrease in lymphocytes were reported for 23% of OND patients and 30% of GRAN-treated patients. A significant increase in neutrophils was seen in 7% of OND-treated patients and 12% of those treated with GRAN. With regard to abnormalities in laboratory data of clinical concern, mean changes in laboratory values from baseline were shown in sponsor's Table 22. Abnormal transaminases were reported in 2 OND patients during the pre-Tx laboratory assessment and in 4 OND patients at the posttreatment laboratory assessment. Although one elevation in transaminases was determined by the investigator to be related to metastases of seminoma, the causality and significance of the majority of these observations were unknown. The mean changes in transaminase values from pretreatment to posttreatment were not clinically significant and were similar among both treatment groups. Of the 154 OND and 156 GRAN patients with pre- and posttreatment transaminase laboratory values, the mean (sd) change in ALT from baseline was 0.9 U/L (40.3) for OND patients and 2.7 U/L (12.9) for patients receiving GRAN. Mean changes (sd) in AST were similar, 0.0 U/L (36.8) for patients receiving ondansetron and 1.3 U/L (16.6) for those receiving granisetron. There was no patient withdrawn due to laboratory abnormalities. The 2 treatment groups were similar with respect to transitions in laboratory parameters. Finally, there were no laboratory abnormalities reported as AEs.

[20] Patients No. 7377 and 7416, both randomized to GRAN in protocol S3AA3004, were consented and randomized, but due to a pharmacy error did not receive test medication.

TABLE 16
Study S3AA3004/3007 (Report RM1997/04252/00)

SUMMARY RESULTS OF SAFETY EVALUATIONS

	OND 24 mg QD PO	GRAN 10 μg/Kg I.V.
Extent of Exposure (n=)	184	187
Median Dose of Cisplatin (mg/m^2)	70	70
Median time of Cisplatin Infusion	2	2
Number of Deaths (Cause)	1 Pt. #301-9051 (Decreased consciousness, cerebrovascular accident) [Unlikely related to test medication]	0
Serious AEs	2 Pt. #301-9051 (see above) Pt. #118-7168 (Severe nausea, vomiting, no appetite and inability to retain orally ingested liquids or solids) [Lack of efficacy]	1 Pt. #126-8876 M.I. [Unrelated to the use of test medication]
Withdrawals due to AEs	2 Pt. #9011 (W/D due to shaking chills, fever, possible UTI, intractable bladder pain, and bladder spasms. All the events resolved) [Not related to test medication] Pt. #9051 (W/D from the trial when the patient could not be aroused from his sleep. The patient died two days later due to CV hemorrhage) [Unlikely related to test medication]	0
Proportion Reporting One or More AE	44 (24%)	52 (28%)
Most Commonly Reported AE: headache	13 (7%)	23 (12%)
Proportion with Treatment-Related AEs	15 (8%)	23 (12%)

Reviewer's Table

The most often occurring treatment-related AEs were neurological, which occurred in 12 of the OND patients (7%) and 19 of the GRAN patients (10%). Neurological treatment related AEs were primarily headache (7% OND, 9% GRAN patients.)

13. Sponsor's Conclusions

"A single oral dose of ondansetron is effective for the prevention of nausea and vomiting induced by highly emetogenic chemotherapy (cisplatin 50-75mg/m^2).

"A single oral dose of ondansetron (24mg) is therapeutically as effective as a single intravenous dose of granisetron (10μg/kg) for preventing nausea and vomiting in subjects receiving highly emetogenic chemotherapy (cisplatin 50-75mg/m^2). There were no statistical differences between oral ondansetron 24mg and intravenous granisetron 10μg/kg in terms of 1) complete response; 2) time to first emetic episode, withdrawal or rescue; 3) posttreatment nausea assessment scores; and 4) posttreatment appetite assessments.

"Both oral ondansetron and intravenous granisetron were shown to be safe and well tolerated. Adverse events and laboratory safety profiles were similar for each treatment group."

14. Reviewer's Additional Comments

Study –3004/3007 is the second study submitted by the sponsor in support of the sought claim: efficacy of oral doses of OND, 24 mg once-a-day for the prevention of N&V associated with highly emetogenic cancer chemotherapy, including cisplatin.

A useful design was used and the trial was carried out with appropriate methodology. This included standardization of the study population (chemotherapy-naive patients that had histologically confirmed diagnosis of cancer and were scheduled to receive cisplatin-based highly emetogenic regimens). Also included were adequate procedures to preserve the nature of the double-blind character of the trial and minimize bias, randomization schemes accomplishing treatment groups comparable to each other in most respects and standardization of emetogenic stimulus. Also standardized were the clinical evaluation endpoints to gather data to be used in the assessment efficacy and safety. Appropriate statistical methodology was utilized to evaluate results so that valid, meaningful conclusions could be drawn.

According to the protocol, this active-active trial was set to test the efficacy – during the acute phase (first 24h post chemotherapy) – of the orally administered 24 mg/day single dose of OND. The control group consisted of a labeled single dose of intravenously administered granisetron (10 μg/Kg) infusion. According to the protocol, the trial was set to demonstrate a therapeutic gain of 15% of one regimen (OND) over the other (GRAN). This expected difference of 15% between the two treatment groups is testing the hypothesis that oral OND 24 mg OD is superior to GRAN 10 μg/Kg I.V. This is an important consideration. If no superiority were to be shown, the demonstration that OND is similar in efficacy to the approved GRAN regimen alone would not suffice because this was not the protocol-stipulated objective of the trial. In that circumstance, an additional trial would be needed. But results of study –3004/3007 are expected to be supportive of those of study –3012.

Many features of study –004/3007 were as those described for study –3012. In study –3004/3007, the study population (ITT=373) consisted of platinum-naive, median age of 65y for the OND group and 66y for the GRAN group, mostly Caucasian, 56% male, 44% females in general without evidence of significant cardiovascular/hepatic disease. The site of primary neoplasm that occurred with the highest frequency was the lung (59%); other types of tumors occurring at lower rates. The randomization procedures were apparently well executed. The result was two treatment population of patients (OND= 184, GRAN= 187) that were comparable to each other wish respect to variables that may influence outcome. For both treatment groups, the demographics, primary disease state, other significant medical conditions, Karnosky status, and prior medications were similar. The two arms of the trial were also balanced with respect to other variables such as concomitant medications that may be confounding, such as concomitant chemotherapy (etoposide=48%, MTX=6% and 5-FU=12%).

In this trial, the two treatment groups were well matched with regard to the standardization of emetogenic stimulus, which consisted primarily of cisplatin (median dose = 70 mg/m^2). This cisplatin regimen is best characterized as being of high emetogenic potential. Also adequate were the clinical procedures and the statistical methodology used to assess efficacy. As in previous trials and study –3012, the primary endpoint of efficacy was complete response (CR) which was derived by adequate and previously validated approaches. Only CR is considered for the purpose of the reviewer's further discussions.

As summarized in Table 15, ITT analyses showed a therapeutic gain of 7% of the 24 mg oral OND OD over the control group (10 μg/Kg GRAN I.V.). The 95% CI were –4%, 17%. This difference was not statistically significant. The Per protocol analyses showed very similar results to those seen in ITT analysis: a 7% therapeutic gain of OND 24 mg over the GRAN arm, with 95% CI of –3% and 18% and - again - lack of statistically significant difference. The results of these statistical evaluations can be interpreted as this trial failing to meet the protocol-stipulated study objective since this study was set to show **superiority** (15%) of OND over the control GRAN. However, it would seem that, all things considered, study –3004/3007 used a design that permitted a valid comparison with an approved control to provide a quantitative assessment of the **drug's effect**. The reviewer considers that this active control trial is not testing the hypothesis that an effect exists. The trial places emphasis on **estimates of effect**. With this consideration in mind, the conclusion is reached that the effect of orally administered 24 mg OND given once-a-day **cannot be differentiated** from that seen with the control group [the approved dose of intravenously administered GRAN (10 μg/Kg)]. In other words, oral doses of OND (24 mg) are effective for preventing nausea and vomiting associated with highly emetogenic cisplatin-based chemotherapy.

In this trial, both oral GRAN and intravenous GRAN were shown to be safe and well-tolerated. AEs and laboratory safety profiles were similar for each treatment group.

V. REVIEWER'S OVERALL CONCLUSIONS ON EFFICACY

Through the submission of NDA 20-103, Ref. No. 015 SE-1, the sponsor is requesting approval for the registration of a 24-mg ZOFRAN® tablet strength. The indication sought is "Prevention of nausea and vomiting associated with highly emetogenic cancer chemotherapy, including cisplatin". In support of their application, the sponsor submitted results of two randomized, double-blind, active comparator, parallel, multicenter trials: -3012 and –3004/3007. These two trials used useful designs, are the subject of the present review and are further considered below. Also submitted as "supportive" were results of a third trial, S3AB3008. But this trial did not use a useful design. Study –3008 attempted to answer too many questions with many variables, such as the experimental role of dexamithesone in combination regimens. Highly emetogenic cisplatin regimen were not consistently used in this hypothesis generating study. Because of these deficiencies in study design it was concluded that this trial was not contributory. As a consequence, results of study –3008 were not reviewed here.

Studies –3012 (3 arms) and –3004/3007 (2 arms) used a useful design and were apparently well-executed. These studies used a design that permitted a valid comparison of the effect of the experimental treatment group with a reasonable control of the same drug, in one study, or an approved control (another drug) in the other study, to provide a quantitative assessment of the drug effect. Both trials were randomized, double-blind, multicenter, acute phase (24h postchemotherapy), comparative trials. The efficacy and safety of the proposed 24 mg oral single ondansetron dose against active comparators were tested in adequate study populations and against highly emetogenic chemotherapy regimens. In both studies, the emetogenic stimulus and the methods to assess efficacy and safety were standardized. Both studies enrolled an apparently adequate number of patients per arm. All these approaches were useful in permitting meaningful conclusions to be drawn.

In study –3012 the control group consisted of 8-mg OND tablets given twice-a-day. This is the recommended adult oral dosage of ZOFRAN® tablets for the prevention of N&V associated with initial and repeat courses of moderately emetogenic cancer chemotherapy. According to the protocol, a therapeutic gain of 20% [OND 24 mg OD (60%) –(minus) – OND 8 mg BID (40%)] and statistical superiority of the test over the control group was expected. Instead, the results of the trial were somewhat disappointing. A therapeutic gain of only 11% was shown in the ITT population and 14% in the Per-Protocol population. The difference between these groups was quasi statistically significantly in analysis of the ITT population ($p=0.053$) and significant in analysis of the Per-Protocol population ($p=0.027$). The third arm in study –3012 consisted of 32 mg oral OND QD, a dose that should be technically considered as experimental. This is because 32 mg OND QD, when administered intravenously, is approved for prevention of N&V induced by highly emetogenic regimens, including cisplatin. But in study -3012 the 32 mg of the drug is being administered orally and not intravenously. At any rate, in the protocol, the 24 mg OND QD PO was expected to be associated with 5% less therapeutic gain than the comparator 32 mg. Instead, both population analyses showed a therapeutic gain (rather than loss) of 11% in favor of the 24 mg OND PO. However, in neither of the population analyses was this difference (11%) statistically significant ($p=0.073$).

From the above results in study –3012, the reviewer concluded that the 24 mg OND QD PO was quasi superior (p=0.053 in the ITT, p=0.,027 in the Per-Protocol population) to one of the comparator arms (8 mg BID) and at least as effective as 32 mg QD (p=0.073). It was also concluded that results of study –3012 with a p-value of 0.053/0.027 were not impressive for a **single study** (alone). This is because the replication probability is 50%. The probability of internal reversal of treatment effect is high. Replication of results in study –3012 is needed because a p-value of 0.053/0.027 in the ITT/Per Protocol population, respectively, does not constitute a very persuasive statistical finding. This study alone is not enough for approval. A confirmatory study is needed to convincingly demonstrate that OND 24 mg/day is indeed efficacious. The reviewer believes that study –3004/3007 (see below) is confirmatory.

Study –3004/3007 consisted of two nearly identical trials that, due to slow enrollment (because the regimens did not contain dexamethasone), were merged and reported as one. The control group consisted of an approved regimen of granisetron for the sought indication. This regimen (10 μg/Kg single dose) was administered intravenously. It is important to note that, according to protocol-stipulated objectives, a therapeutic gain of 15% (OND > GRAN) was expected and, therefore the study was set to test the hypothesis that one drug is superior to the other. This is an important consideration. When analyses of the results did not show superiority, the sponsor reported the findings as if the trial had been designed to show equivalence. In his evaluations, the reviewer usually put emphasis on results Per-Protocol rather than ITT analyses to demonstrate equivalence. But in this instance, it makes no difference because the statistical analysis in one or the other study populations rendered the same conclusions. Instead of the expected difference of 15% (which may have demonstrated superiority of OND over GRAN), a therapeutic gain of only 7% was shown in both study populations. Based on these results, the 24 mg OND QD PO dose **appears** to be equivalent (but most certainly not superior) to the active GRAN comparator. Just as study –3012, this second trial (-3004/3008), estimated the treatment effect rather than tested the hypothesis that an effect exist. Nonetheless, the reviewer uses the word "appears" because this demonstration of equivalence was an afterthought, a post-hoc evaluation carried out when the trial did not show superiority. The reviewer concluded that although the results of the post-hoc analysis of study –3004/3008 are supportive of those in study –3012 above, they **cannot stand alone**. In other words, a prospectively designed trial set to demonstrate equivalence is needed in order for the sponsor to be able to claim that a single daily dose of 24 mg of ondansetron administered orally is **equivalent in efficacy** to 10 μg/Kg of intravenous granisetron (the approved dose regimen of this drug).

In summary, all in all, the results of study –3012 together with those of –3004/3008 are sufficient to establish that the orally administered 24 mg OND one-a-day dose level is efficacious. Further demonstration that the effect of OND is no worse than that of the GRAN comparator was the finding of identical CR (70%) for both treatment groups in the center enrolling the most patients (n=60) in this trial.

In addition, in both pivotal trials, the response rate of the 24 mg OND QD PO (66% CR rate in study –3012 and 58% CR rate in study –3004/3008) was superior to a historical placebo CR rate (0% to 22%) in patients receiving highly emetogenic chemotherapy [Review of January 12, 1998 of IND [redacted].

VI. REVIEWER'S OVERALL CONCLUSIONS ON SAFETY

In study –3012 graded doses of ondansetron, whether 8 mg BID, 24 mg once-a-day or 32 mg once-a-day were safe and well-tolerated. Similarly, in study –3004/3008 both oral granisetron (24 mg/day) and intravenous granisetron (10 μg/Kg) were shown to be safe and well-tolerated. In all clinical trials, AEs and laboratory safety profiles were similar for each treatment group.

VII. RECOMMENDATIONS FOR REGULATORY ACTION

1. Approval is recommended for the marketing of 24 mg single dose of orally administered ondansetron for the prevention of nausea and vomiting associated with highly emetogenic cancer chemotherapy, including cisplatin.

2. It is also recommended **not to allow** the sponsor to claim that – for this indication - this regimen of orally administered ondansetron (single dose of 24 mg/day) is equivalent in efficacy to the recommended dose regimen of intravenously administered granisetron (10 μg/Kg). For such a claim, evidence from an independent study is needed to confirm the initial equivalence finding reported in study –3004/3007. This trial was set to show superiority of OND over GRAN. When the results showed a therapeutic gain of only 7% instead of the protocol-stipulated 15%, the Clinical Report addressed equivalence without considering superiority.

3. Minimum revisions to the currently approved labeling are recommended. It might be noted that the 24 mg QD PO ondansetron dose level was shown to be efficacious by a) demonstrating superiority to a lower daily dose of the drug in one trial and b) by showing equivalence to a dose regimen of an approved 5-HT_3 receptor antagonist in another trial.

February 19, 1999

/S/ [redacted]

Hugo E. Gallo-Torres, M.D., Ph.D.

cc:
NDA 20-103
HFD-180
HFD-180/LTalarico /S/ [redacted] 2-19-99
HFD-180/HGallo-Torres